ISSN 1936-8798/08/$34.00
PUBLISHED BY ELSEVIER
DOI: 10.1016/j.jcin.2007.11.009

Evaluation of a Novel Slow-Release Paclitaxel-Eluting Stent With a Bioabsorbable Polymeric Surface Coating

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Objectives We sought to evaluate a new second-generation drug-eluting stent (DES), comprising a slow-release biodegradable polylactide coglycolide (PLGA) polymer and low-dose paclitaxel on a thin-strut cobalt chromium stent platform, in a clinically relevant animal model.

Background Our previous work demonstrated subacute vascular toxicity and necrosis triggering late excess neointima in pig coronaries, with a moderate paclitaxel dose eluted from an erodible polymer. The use of slower-releasing absorbable polymers with lower doses of paclitaxel is expected to minimize such adverse outcomes.

Methods Three types of stents were implanted in pig coronary arteries using quantitative coronary angiography to optimize stent apposition: bare-metal stents (BMS); absorbable, slow-release polymer-coated-only stents (POLY); and absorbable polymer-based paclitaxel-eluting stents (PACL). The dose density of paclitaxel was 0.15 $\mu g/mm^2$ with in vitro studies demonstrating a gradual elution over the course of 12 to 16 weeks. Animals underwent angiographic restudy and were terminated at 1 and 3 months for complete histopathologic and histomorphometric analyses.

Results At 1 month, intimal thickness varied significantly according to stent type, with the lowest level for the PACL group compared with the BMS and POLY groups (0.06 ± 0.02 mm vs. 0.17 ± 0.07 mm, 0.17 ± 0.08 mm, respectively, $p < 0.001$); histological percent area stenosis was 18 ± 4% for PACL compared with 27 ± 7% for BMS and 30 ± 12% for POLY, respectively ($p = 0.001$). At 3 months, PACL showed similar neointimal thickness as BMS and POLY (0.09 ± 0.05 mm vs. 0.13 ± 0.10 mm and 0.11 ± 0.03 mm respectively, $p = 0.582$). Histological percent area stenosis was 23 ± 8% for PACL versus 23 ± 11% for BMS and 23 ± 2% for POLY, respectively ($p = 1.000$).

Conclusions This study shows favorable vascular compatibility and efficacy for a novel DES that elutes paclitaxel in porcine coronary arteries. These results support the notion that slowing the release rate and lowering the dose of paclitaxel favorably influences the vascular biological response to DES implant, decreasing early toxicity and promoting stable healing while still suppressing neointima formation. (J Am Coll Cardiol Intv 2008;1:81–7) © 2008 by the American College of Cardiology Foundation

From *Saint Joseph's Cardiovascular Research Institute/Saint Joseph's Hospital of Atlanta, Georgia; and †DISA Vascular Ltd., Cape Town, South Africa. Supported by a research grant from DISA Vascular Ltd., but all contents are solely the responsibility of the authors. Mr. Conway and Dr. Molema are employees and shareholders of DISA Vascular.

Manuscript received August 22, 2007; revised manuscript received November 26, 2007, accepted November 29, 2007.

Our previous work (1) demonstrated the potential for profound subacute vascular toxicity and necrosis followed by severe late rebound neointimal fibrosis in porcine coronary arteries with a moderate dose (0.3 $\mu g/mm^2$) of paclitaxel eluted from a nonpermanent, erodible polymer. Other investigators have also shown that the rapid release of paclitaxel, although effective in suppressing medium-term in-stent fibrocellular neointima formation, can evoke necrosis, stent malapposition, and delayed healing (2,3). These phenomena, observed in the animal model—with or without potential hypersensitivity and long-term drug leaching from permanent polymer coatings, as well as thick-strut stent platforms—may be related to adverse late clinical events such as late stent thrombosis in paclitaxel- and sirolimus-coated stents (4–9). Hence, we investigated the use of a slower-releasing absorbable polymer with lower doses of paclitaxel on a thin-strut stent platform for its capacity to eliminate such adverse outcomes while maintaining neointimal suppression. Our objective in this study was to evaluate a new second-generation drug-eluting stent (DES) comprising an erodible polymer and low-dose paclitaxel on a thin-strut cobalt chromium stent platform, in a clinically relevant porcine coronary artery model.

Abbreviations and Acronyms

ANOVA = analysis of variance
BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
EEL = external elastic lamina
IEL = internal elastic lamina
PACL = polymer-based paclitaxel-eluting stent(s)
PLGA = polylactide coglycolide
POLY = polymer-only-coated stent(s)

Methods

Study design. Nineteen juvenile domestic pigs (28 to 44 kg) were enrolled in this study. Experimental procedures were performed in a standard fashion without notable difficulties according to the recommendations of the consensus advisory panel to the Food and Drug Administration (10) and in compliance with the Association for Accreditation of Laboratory Animal Care guidelines. Stents were implanted according to a randomization scheme to provide even distribution across the 3 epicardial arteries, constrained by individual anatomy, to reduce potential bias from unique arterial implant site responses.

A total of 55 stents of 3 different types; bare-metal stents (BMS), bioabsorbable polymer-only-coated stents (POLY), and bioabsorbable polymer-based paclitaxel-eluting stents (PACL) were implanted in pig coronary arteries. The ChromoFlex (DISA Vascular, Cape Town, South Africa) thin-strut cobalt chromium stent of 3.0 mm diameter and 11 mm length was the platform for all stents.

Animals, stent implant, terminal restudy, and sample preparation. Animals received 81 mg aspirin and 75 mg clopidogrel 3 days before implant and daily until termination. Cardiac catheterization was performed with full heparinization (200 U/kg), and stents were implanted using quantitative coronary angiography (QCA) to obtain a stent to artery ratio $\approx$ 1.1:1. Post-implant angiography and QCA were performed to determine stent size, complete apposition, and patency. Stent to artery ratios by QCA were similar among groups: 1.11 $\pm$ 0.05, 1.12 $\pm$ 0.04, and 1.09 $\pm$ 0.07 for BMS, POLY, and PACL, respectively (p = NS).

Thirteen pigs were sacrificed after 1 month and 6 pigs after 3 months. At explant, coronary arteries were perfusion-rinsed with phosphate-buffered saline and perfusion-fixed in situ at physiologic pressure with 5% formalin/1.25% glutaraldehyde for 15 to 20 min. Stented vessels were trimmed free from the heart and embedded in methyl methacrylate. Sections from proximal, middle, and distal vessel regions were cut using a heavy-duty microtome, collected on glass slides, deplasticized, and stained with hematoxylin and eosin and Movat-pentachrome.

Polymer formulation and drug loading. The biodegradable polymer used on the DES system was PLGA (polylactide coglycolide), a co-polymer of polyglycolide and polylactide, which are aliphatic polyesters of the poly(α-hydroxy acids), glycolic and lactic acid. Polylactide coglycolide is hydrophilic and undergoes bulk erosion as water enters the polymer bulk and hydrolytic degradation occurs. Bulk erosion results in polymer surfaces with multiple concavities. There exists an extensive range of possible polyglycolide/polylactide ratios, and this, together with the variable molecular weight for a given ratio, provides a wide range of possible degradation and, hence, elution rates.

Stents were coated by dissolution of PLGA and paclitaxel in a fixed ratio; the drug was Good Manufacturing Practice grade (purity 99.7%). A polymer or polymer/drug mixture was sprayed onto the stents and dried to constant mass. Paclitaxel content was determined by gravimetric analysis with verification by coating dissolution and high-performance liquid chromatography.

The in vitro bioerosion of PLGA is known to be slower than in vivo elution, which is attributed to the presence of biological compounds in the latter environment—especially lipids and enzymes—which contribute to faster breakdown, and, hence, the likely faster drug elution (11). In vitro release kinetics were determined on expanded stents immersed in 2-ml aliquots of agitated phosphate-buffered saline at 37°C for 50 days. The buffer was changed every 2 to 3 days, and the paclitaxel content determined with high-performance liquid chromatography. The biodegradable polymer had a 6- to 10-μm coating thickness, and the DES held a drug dose density of 0.15 $\mu g/mm^2$ of stent surface area or 0.89 $\mu g/mm$ of stent length.

Histopathology. Distal, middle, and proximal sections from each of the stented coronary arterial segments were scored for inflammation, necrosis, intramural hemorrhage, and

mural thrombus. The nature of the extracellular matrix in the neointima and adventitia was assessed and described. An overall inflammation score was assigned according to the following semiquantitative grading scale: 0 = none; 1 = mild, scattered inflammatory cells; 2 = moderate, inflammatory cells encompassing <50% of a strut in at least 25% to 50% of the circumference of the artery; and 3 = severe, inflammatory cells surrounding a strut in at least 25% to 50% of the circumference of the artery (12). A scoring scale was used to grade the extent of vessel injury determined by stent strut penetration into the vessel wall as follows: 0 = strut not in contact with internal elastic lamina (IEL); 1 = strut contacting IEL with profile in neointima; 2 = strut penetrating IEL and profile in media; 3 = strut penetrating media and contacting external elastic lamina (EEL); and 4 = strut in adventitia (13).

Histomorphometry. Sections were imaged with 20× instrument magnification. Morphometric analysis was performed by computerized planimetry on all levels of all stents. Lumen, IEL, and EEL were traced and area measurements obtained; areas of neointima and media were obtained by subtraction. Neointimal thickness at each stent strut was measured. Histologic percent area stenosis (1 − [luminal area/IEL area] × 100) was calculated.

Statistical analysis. Descriptive statistics were generated for all quantitative data and expressed as mean ± SEM. Histomorphometric data were evaluated with 1-way analysis of variance (ANOVA). All-pairwise multiple comparisons with the Tukey method were performed if ANOVA probability was <5%. For noncontinuous data (i.e., histopathologic scoring), Kruskal-Wallis 1-way ANOVA on ranks was used.

Results

Angiographic restudy, histopathologic and histomorphometric measurements, and analyses were completed on 55 stents from 19 animals. Table 1 illustrates the distribution of stents according to stent type and restudy time.

In vitro drug-release pharmacokinetics. The release profile for the slow release polymer with a low total drug load is shown in Figure 1. There is an initial mild burst for the first 20 days as the paclitaxel on the coating surface is released,

Table 1. Distribution of Stented Vessel Samples According to Stent Type and Restudy Time

Stent Type	1 Month	3 Months	Total
PACL	15	7	22
BMS	12	5	17
POLY	11	5	16
Total	38	17	55

BMS = bare-metal stents; PACL = polymer-based paclitaxel-eluting stents; POLY = polymer-only coated stents.

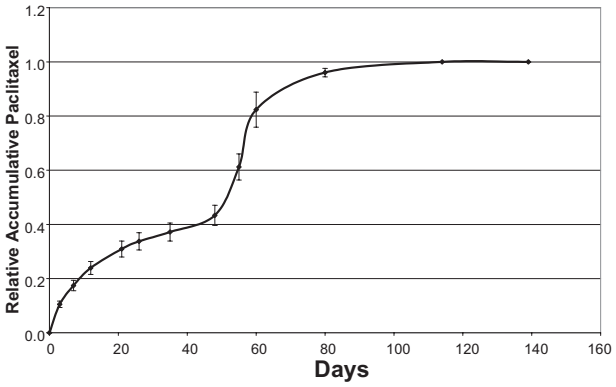

Figure 1. Elution Profile of Paclitaxel From Bioabsorbable Coating

Elution of paclitaxel in saline at 37°C from bioabsorbable coating on 5 samples of cobalt chromium stents. A mild burst-release for 20 days is followed by more gradual release; a subsequent increase in release rate after 50 days subsides as >90% of drug has eluted.

followed by a period of moderate release, which is believed to correspond to diffusion of the drug out of the hydrated but intact polymer. This diffusion release phase then flattens out, and a subsequent increase in release rate after 50 days corresponds to an increase in the erosion rate of the polymer, which finally tapers off again as 90% or more of the drug has eluted.

Angiographic follow-up. At 1 month, the angiographic percent stenosis was significantly lower for PACL compared with the BMS and POLY groups (2 ± 2% vs. 12 ± 4% and 11 ± 10%, respectively, $p < 0.001$) (Fig. 2). There was no difference between the BMS and POLY groups ($p = 0.914$). At 3 months, there was no difference in angiographic percent stenosis between the PACL versus BMS

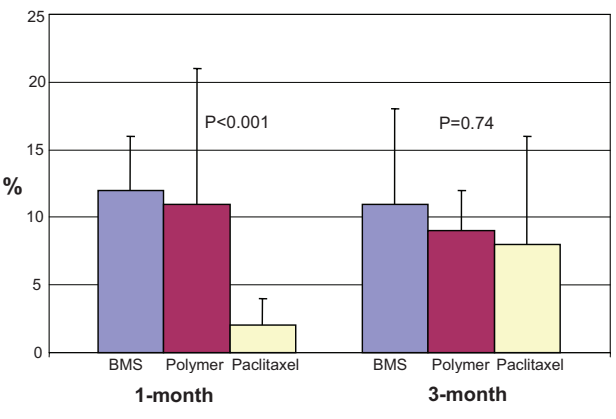

Figure 2. Angiographic Percent Diameter Stenosis at 1 and 3 Months

Angiographic percent diameter stenosis at 1 and 3 months' follow-up in stented pig coronary arteries according to treatment group. BMS = bare-metal stent.

and POLY groups (8 ± 8% vs. 11 ± 7% and 9 ± 3%, respectively, p = 0.745) (Fig. 2). There was no significant progression of angiographic percent stenosis in all treatment groups from 1 to 3 months (BMS, p = 0.8527; POLY, p = 0.7526; and PACL, p = 0.1195).

Histopathology and histomorphometry. **QUALITATIVE OBSERVATIONS.** For 1-month stent implants, there was a wide range of coronary artery biological responses between groups. The anticipated response to BMS was observed, with generally mild vessel wall stent-associated injury in the form of medial compression subjacent to stent strut sites of contact with the internal lamina, and thin to moderately thick concentric fibrocellular neointima formation with complete coverage of flattened periluminal cells (Figs. 3 and 4). Inflammatory response was generally minimal, with occasional foreign body giant cells and only rare focal more florid infiltrates. When present, the latter were primarily histiolymphocytic in nature. There was only minimal adventitial reaction, and it appeared mostly in the form of fibrotic thickening. The 1-month response to POLY was indistinguishable from BMS. For the slow-release PACL group, there was only minimal medial necrosis and virtually no hemorrhage, and stent malapposition was not observed. The neointima was attenuated; fibrinoid deposits and inspissated thrombus were present localized to the stent struts, but there were spindle-shaped cells in the neointima between strut profiles and near the luminal surface. The inflammatory response to PACL was somewhat greater than for BMS and POLY.

At 3 months, vessel wall healing had progressed in all groups. For BMS and POLY, there were fewer changes and, in general, the only notable finding was that the neointima had become somewhat thinned, contained more collagen and less proteoglycan, and the intimal cells were more closely arranged with a greater proportion of spindle-

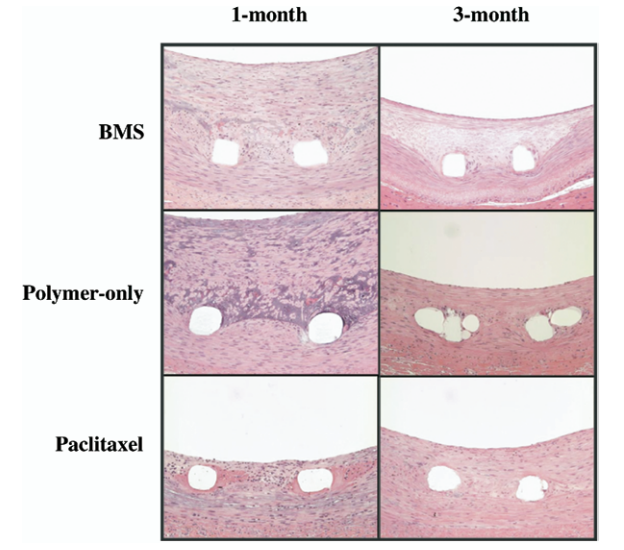

Figure 4. High-Magnification Microscopic Images of Sections From 1- and 3-Month Samples

High-magnification microscopic images of hematoxylin and eosin-stained sections from pig coronary arteries fixed 1 and 3 months after stent implant. Note thin neointima with some residual fibrin deposits, but no media necrosis for the paclitaxel-eluting stent at 1 month and well-healed arterial wall response for this stent at 3 months. BMS = bare-metal stent.

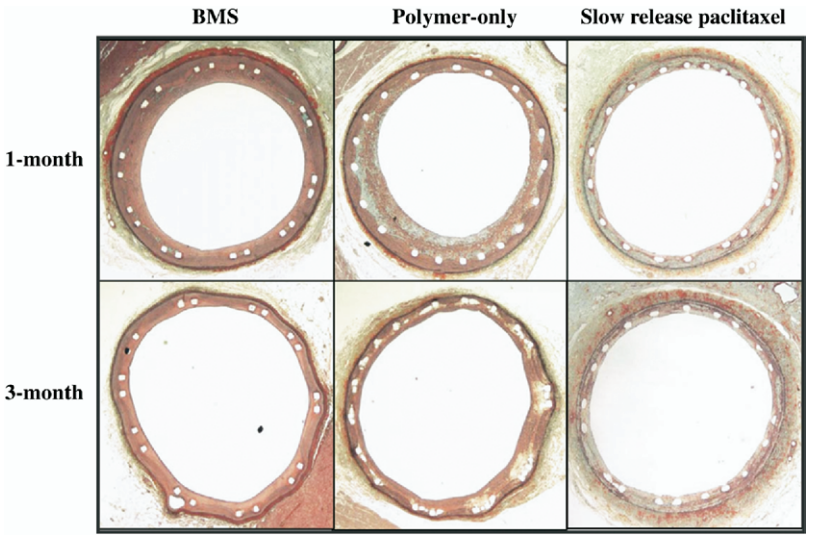

Figure 3. Low-Magnification Microscopic Images of Sections From 1- and 3-Month Samples

Low-magnification microscopic images of Movat-stained sections from 1- and 3-month samples demonstrating comparative overall vessel morphologies, with thinner neointima for the paclitaxel-eluting stent at 1 month. BMS = bare-metal stent.

shaped rather than stellate or round cells. Also, for POLY, voluminous neovascular channels were found closely localized to the stent struts that were not observed in BMS. In the PACL group, the neointima was generally thin and concentric with a fibrocellular structure; small inspissated thrombus and/or fibrinoid deposits were seen closely abutted to the stent struts. Inflammation was minimal for this group and consisted primarily of rare leukocytes at the luminal blood flow interface. The periluminal cell layer in all groups was flattened and contiguous.

MEASURED AND SCORED VARIABLES. Histopathologic and histomorphometric descriptors of vessel responses were found to vary according to stent type and restudy time, substantiating and quantifying the morphological qualitative observations. These descriptors included intimal thickness, histological percent stenosis, inflammation score, and strut injury score. Illustrative micrographs of vessel responses are shown in Figure 3.

INTIMAL THICKNESS. At 1 month, intimal thickness was significantly lower for the PACL group compared with the BMS and POLY groups (0.06 ± 0.02 mm vs. 0.17 ± 0.07 mm and 0.17 ± 0.08 mm, respectively, $p < 0.001$) (Fig. 5). There was no difference in intimal thickness between the BMS and POLY groups ($p = 1.000$). At 3 months, the PACL group showed similar neointimal thickness as the BMS and POLY groups (0.09 ± 0.05 mm vs. 0.13 ± 0.10 mm and 0.11 ± 0.03 mm, respectively, $p = 0.582$) (Fig. 5). There was no significant progression of intimal thickness in all treatment groups from 1 to 3 months (BMS, $p = 0.4669$; POLY, $p = 0.1311$; and PACL, $p = 0.1565$).

HISTOLOGICAL PERCENT AREA STENOSIS. At 1 month, histological percent stenosis varied significantly according to stent type, with the lowest level for the PACL group compared with the BMS and POLY groups (18 ± 4% vs. 27 ± 7% and 30 ± 12%, respectively, $p = 0.001$) (Fig. 6). There was no difference in histological percent stenosis between the BMS and POLY groups ($p = 0.640$). At 3 months, the PACL group showed similar histological percent stenosis as the BMS and POLY groups (23 ± 8% vs. 23 ± 11% and 23 ± 2%, respectively, $p = 1.000$) (Fig. 6). There was no significant progression of histological percent stenosis in all treatment groups from 1 to 3 months (BMS, $p = 0.4846$; POLY, $p = 0.0945$; and PACL, $p = 0.0945$).

INFLAMMATION AND STRUT INJURY SCORES. The PACL group tended to have a greater inflammation score (mild to moderate) compared with the BMS and POLY groups (mild) at 1 and 3 months (Table 2). The strut injury score was low and similar between the groups at 1 and 3 months (Table 3).

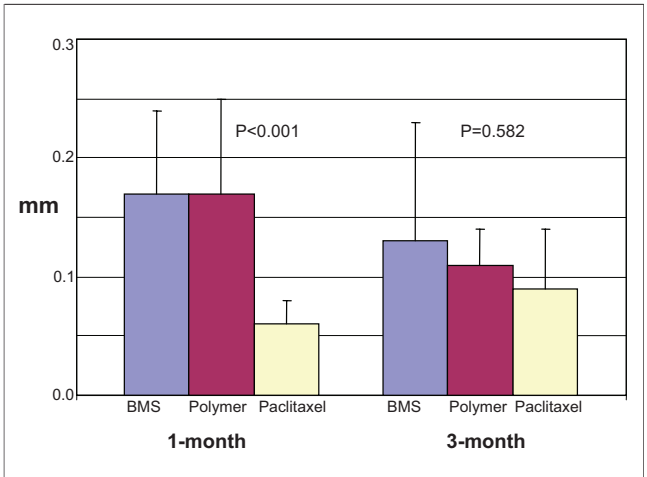

Figure 5. Intimal Thickness of Tissue Overlying Stent Struts at 1 and 3 Months

Intimal thickness of tissue overlying the stent struts, measured from histologic sections of porcine coronary arteries harvested at 1 and 3 months after stent implant, according to treatment group. BMS = bare-metal stent.

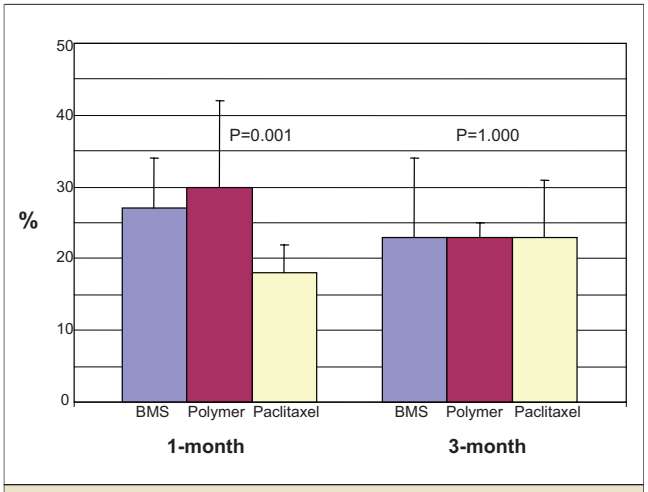

Figure 6. Histological Percent Area Stenosis at 1 and 3 Months

Proportion of area within stent occupied by neointimal tissue (% stenosis) measured from histologic sections of porcine coronary arteries harvested at 1 and 3 months after stent implant, according to treatment group. BMS = bare-metal stent.

Discussion

Our results confirm that stent-bound paclitaxel is effective in suppressing neointima formation in stented porcine coronary arteries at the classic 1-month time point. Furthermore, our data suggest that the rate of delivery of the drug to the vascular tissue (as well as the total drug dose) is an important determinant of the overall arterial response.

In parallel experiments, we also examined the impact of individually reducing either the drug dose or the release rate. These pilot investigations indicated a greater importance for release rate rather than total drug dose, as the primary determinant of early coronary toxicity in pigs

Table 2. Histopathologic Scoring of Inflammation in the Treatment Groups by Time

	1 Month			3 Months		
Stent Type	**BMS (n = 12)**	**POLY (n = 11)**	**PACL (n = 15)**	**BMS (n = 5)**	**POLY (n = 5)**	**PACL (n = 7)**
Grade 0	0	0	0	0	0	0
Grade 1	10 (83%)	9 (82%)	5 (33%)	5 (100%)	5 (100%)	5 (71%)
Grade 2	2 (17%)	2 (18%)	10 (67%)	0	0	2 (29%)
Grade 3	0	0	0	0	0	0

Inflammation score: 0 = none; 1 = mild; 2 = moderate; 3 = severe. Data represent n (%) of overall scores for scoring category and stent type.
Abbreviations as in Table 1.

(data not shown). Accordingly, we designed the present study to assess whether the combination of these modifications could preserve antineointimal efficacy while reducing toxicity and enhancing a long-term stable healing response. The results verify that this combination was effective for both outcomes.

Even at moderate and low total drug doses of paclitaxel, a fast-release kinetic can elicit a profound toxic response with considerable medial necrosis and stent malapposition at 1 month followed by an aggressive late neointimal "catch-up" at 3 months. It is understood that, despite limitations, the reaction of normal porcine coronary arteries to stent implantation at 1 month is reasonably similar to human coronary responses at much later time points, such as 6 months (5). Although we have shown in our previous work that a faster release kinetic is locally toxic in porcine coronaries at 1 month, there was nevertheless a widely patent lumen seen angiographically and histologically at this time point. Similarly, in the clinical trials of first generation paclitaxel- and sirolimus-eluting stents, evidence of "black holes" (14), "peristent" tissue (15), and late acquired stent malapposition (16) underscores the possibility that a widely patent lumen at 6 months may belie a healed, stable arterial wall. Necrosis of the smooth muscle cells in the tunica media likely triggers a loss of vascular tone with consequent distention/ectasia and separation of the vessel wall from the stent struts. Thrombus then fills in the void between the stent and the dilated vessel wall. Although this toxicity may be masked or reduced in diseased human coronaries, it seems plausible that at least some DES may achieve restenosis reduction at 6 months by a similar mechanism. The recovery period in humans may be as long as 18 months or even longer (17). Exposed stent struts and thrombus that we have shown at 1 month in pig coronaries (putatively equivalent to the 6-month point in humans) (5) may therefore provide an early marker for potential late DES thrombogenicity in the clinical setting.

We have shown furthermore in the present study that slowing the rate of paclitaxel release can mitigate toxic effects while still achieving a significant attenuation of neointima at 1 month. Although at 3 months, neointima suppression is not maintained in the animal model, there is no aggressive "rebound overshoot" neointima formation, as previously observed, but only a moderate "catch-up" to the control stent levels, and the histological markers of fibrin and endothelial-like coverage suggest a progressive stabilization and healing of the vessel over this period.

Study limitations. The relatively small numbers of animal subjects should be considered and the statistical analysis of data viewed accordingly when interpreting these results. Animal models do not precisely simulate responses to DES in humans (17). We did not perform in vivo pharmacokinetics, which may have provided correlative information to our histological observations and in vitro drug release measurements. Nevertheless, the in vitro data were sufficient to identify differences in relative rates of paclitaxel elution between polymers with different degradation rates. The in vitro data correspond with marked differences in coronary arterial responses between fast- and slow-release polymers.

Table 3. Strut Injury Scoring in the Treatment Groups by Time

	1 Month			3 Months		
Stent Type	**BMS (n = 12)**	**POLY (n = 11)**	**PACL (n = 15)**	**BMS (n = 5)**	**POLY (n = 5)**	**PACL (n = 7)**
Grade 0	3 (25%)	0	12 (80%)	3 (60%)	2 (40%)	5 (71%)
Grade 1	9 (75%)	5 (100%)	3 (20%)	2 (40%)	3 (60%)	2 (29%)
Grade 2	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0

Abbreviations as in Table 1.

Conclusions

Favorable vascular compatibility and efficacy for a novel second-generation DES that elutes paclitaxel from a slow-release bioabsorbable polymeric surface coating were demonstrated in pig coronary artery stent implants. Our results furthermore suggest that the rate of release is a major determinant of toxicity and support the notion that the total dose of paclitaxel may be less relevant in this regard. The specific formulation of a bioabsorbable polymer and the associated drug elution profile profoundly influence the outcome of paclitaxel efficacy and toxicity in the pig model of coronary in-stent restenosis.

Acknowledgments

The authors would like to thank Audrius Abrutis for his assistance with the project management; Cindy Baranowski and Connie Micko for their expert technical assistance with the histologic section preparation; Jourdan Davis for her support with the stent implant procedures; Addrena Taylor for her assistance with the necropsy and tissue preparation; as well as Johnail Arrington and Traci Goodchild, PhD, for their contribution to the histomorphometric measurements.

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